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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/843,250	04/26/2001	Rebecca Parales	875.006US2	7359

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EXAMINER

RAMIREZ, DELIA M

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 03/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/843,250

Applicant(s)

PARALES ET AL.

Examiner

Della M. Ramirez

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 December 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-13 and 30-38 is/are pending in the application.
- 4a) Of the above claim(s) 38 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-13 and 30-37 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

Status of the Application

Claims 1-13, 30-38 are pending.

In response to a supplemental restriction submitted in Paper No. 12, mailed on 11/1/2002, Applicants have elected with traverse the invention of Group I, claims 1-12, 31-37 drawn to a NDO complex comprising the alpha subunit as set forth in SEQ ID NO: 2, 32, 33, 34, 35, or 36. It is noted that claim 30 was inadvertently omitted from Group I, therefore, it is hereby rejoined for examination.

Applicant's traverse is on the ground(s) that a 30-way restriction requirement places an undue burden on Applicants and that the examination of the entire application can be made without serious burden to the Examiner.

Applicant's arguments have been fully considered but are not deemed persuasive to withdraw the restriction requirement. A comprehensive search of all the patentably distinct inventions claimed in the instant application would require a sequence search of each of the proteins recited in the claims which is not co-extensive, patented and non-patented literature searches, as well as a class/subclass search. Therefore, search of all the inventions in the present application would impose an undue burden upon the Examiner and the Office. It is noted however that upon searching SEQ ID NO: 2, it was found that SEQ ID NO: 14 and 15 are identical to SEQ ID NO: 2. In fact SEQ ID NO: 2, 14, and 15 all have the same number of amino acid residues. As such, claim 13 will also be rejoined for examination since it is also partially drawn to a NDO complex comprising the polypeptide of SEQ ID NO: 2.

The requirement is deemed proper and therefore is made FINAL.

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Claim 38 is withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Specification

1. The disclosure is objected to because a brief description of the drawings is missing.

Appropriate correction is required.

Priority

2. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 119(e) to provisional application No. 60/105,575 filed on 10/26/1998.
3. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 120 or 121 to PCT/US99/25079.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on 10/1/2001 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Drawings

5. The drawings have been reviewed and are objected under 37 CFR 1.84 or 1.152. See attached Notice of Draftsperson's Patent Drawing Review. Applicant is required to submit the drawing corrections within the time period set in the attached Office communication. See 37

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CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDONMENT of the application. In addition, if amendments to the specification are needed due to drawing corrections, Applicant is requested to submit such amendments while the case is being prosecuted to expedite the processing of the application.

Claim Objections

6. Claims 1-7, 11-12, 30-37 objected to because of the recitation of “NDO”. Abbreviations unless otherwise obvious and/or commonly used in the art, should not be recited in the claims without at least once reciting the entire phrase for which the abbreviation is used. It is suggested that the term “naphthalene dioxygenase “ be used at least once. Appropriate correction is required.

7. Claim 13 is objected to because it is partially drawn to non-elected inventions. As indicated above, SEQ ID NO: 14 and 15 are identical to SEQ ID NO: 2. In view of this, it will be assumed that claim 13 is also partially drawn to the polypeptide of SEQ ID NO: 2. Examination of such claim will be restricted to the subject matter elected, as described above. Appropriate correction is required.

8. Claims 9-10, 13 are objected to because of the recitation of “has or comprises” since the term “comprises” implies “has”, making the recitation of both “has or comprises” redundant. If Applicant’s intended meaning of the term “has” is “consisting of”, it is suggested that the term “has” be replaced accordingly. If no further limitations are intended, it is suggested that the term “has” be deleted. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-13, 30-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claims 1, 5-7 (claims 2-4, 8-13, 30-37 dependent thereon) are indefinite in the recitation of "NDO related complex" for the following reasons. While the specification (page 10, line 30-page 11, line 4) discloses that the term, in its broadest interpretation, relates to a complex that belongs to the same family of bacterial enzymes as naphthalene dioxygenase (NDO) or toluene dioxygenase (TOD), the term is unclear since one cannot establish which family of bacterial enzymes is being referred to or which are the members of such family. NDO or TOD can belong to the generic family of dioxygenases, to a family of dioxygenases which can catalyze specific types of reactions or a family of dioxygenases which use specific types of substrates. For examination purposes, the term "NDO related complex" will be interpreted as "any dioxygenase complex". Correction is required.

12. Claims 1-8, 11-12, 30-37 are indefinite in the recitation of "position 352, 201, 202, 260, 316, 351, 358, 362, or 366" as it is unclear which position are being referred without indicating the specific sequence to which the recited positions are associated to. Since the claim reads on any NDO complex or any dioxygenase complex (see interpretation of NDO-related complex above), there is no specific sequence associated with positions 352, 201, 202, 260, 316, 351, 358, 362, or 366. It is suggested that applicants amend the claim to include a numerical

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sequence identifier (SEQ ID NO: #) if the sequence has been disclosed in the sequence listing or to clearly identify the sequence to which the recited positions are associated to in the claims.

For examination purposes, no patentable weight will be given to the positions recited in the claims, therefore the claims will be interpreted as being drawn to any NDO or any dioxygenase comprising an alpha subunit which has been substituted anywhere. Correction is required.

13. Claims 1-7 (claims 8-13, 30-37 dependent thereon) are indefinite in the recitation of “catalytically active fragment thereof” for the following reasons. While the specification (page 11, lines 5-15) discloses that the term, in its broadest interpretation, refers to a variant or fragment which catalyzes one or more of the reactions catalyzed by NDO or an NDO-related polypeptide, the term is unclear since one cannot establish which are the reactions being catalyzed by NDO-related polypeptides. As indicated above, the term “NDO-related complex (or polypeptide)” is indefinite, therefore the reactions catalyzed by the fragment cannot be determined. For examination purposes, the term will be interpreted as “any fragment thereof”. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 1-8, 11-12, 30-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

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convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

16. Claims 1-8, 11-12, 30-37 are directed to genera of naphthalene dioxygenase or dioxygenase complexes comprising at least one alpha subunit which has been substituted anywhere, or fragments thereof. See claim interpretation in claim rejections under 35 USC 112, second paragraph. The specification discloses a *Pseudomonas* NDO (Swiss Prot accession number P23094, page 4, lines 25-30) wherein the phenylalanine residue at position 352 has been substituted with valine (SEQ ID NO: 2), glycine (SEQ ID NO: 32), alanine (SEQ ID NO: 33), threonine (SEQ ID NO: 34), leucine (SEQ ID NO: 35), or isoleucine (SEQ ID NO: 36) (Table 7, page 40). The specification also discloses amino acid substitutions at positions 201, 202, 260, 316, 351, 358, 362 and 366 in the alpha subunit of this *Pseudomonas* NDO. In addition, the specification discloses a few dioxygenases which share some structural similarity with NDO (Table 2, page 17). However, there is no disclosure of other NDOs or dioxygenases comprising any substitution in the alpha subunit, as encompassed by the claims, nor there is disclosure of the critical structural elements any polypeptide/complex should have to display NDO or dioxygenase activity. Furthermore, there is no disclosure of which amino acids can be substituted in those polypeptides and preserve function or which is the function of the fragments as encompassed by the claims.

While one could argue that NDOs or dioxygenases are adequately described since one can isolate these enzymes by sequence comparison using the polypeptide structures disclosed in the instant application or the prior art, the state of the art teaches that sequence comparison alone should not be used to determine a protein's function and that small amino acid changes can

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drastically change the function of a polypeptide. Bork (Genome Research, 10:398-400, 2000) teaches protein function is context dependent, and both molecular and cellular aspects must be considered (page 398). Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one amino acid substitution transforms a β -ketoacyl synthase into a malonyl decarboxylase and completely eliminates β -ketoacyl synthase activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. (Science 282:1315-1317, 1998) teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. The specification only discloses a few species of the genera which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of all species within the genera. Thus, one skilled in the art cannot reasonably conclude that Applicant had possession of the claimed invention at the time the instant application was filed.

17. Claims 1-8, 11-12, 30-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the *Pseudomonas* NDO which corresponds to Swiss Prot accession number P23094, wherein (1) the phenylalanine residue at position 352 has been substituted with valine (SEQ ID NO: 2), glycine (SEQ ID NO: 32), alanine (SEQ ID NO: 33), threonine (SEQ ID NO: 34), leucine (SEQ ID NO: 35), or isoleucine (SEQ ID NO: 36) or (2) the residues at positions 201, 202, 260, 316, 351, 358, 362 or 366 in the alpha subunit have been substituted, does not reasonably provide enablement for any NDO or any dioxygenase with any

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substitution. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

The scope of the claims is not commensurate with the enablement provided by the specification in regard to the extremely large number of unknown NDOs or dioxygenases, and fragments thereof, encompassed by the claims. While the specification discloses the *Pseudomonas* NDO which corresponds to Swiss Prot accession number P23094, wherein (1) the phenylalanine residue at position 352 has been substituted with valine (SEQ ID NO: 2), glycine (SEQ ID NO: 32), alanine (SEQ ID NO: 33), threonine (SEQ ID NO: 34), leucine (SEQ ID NO: 35), or isoleucine (SEQ ID NO: 36) or (2) the residues at positions 201, 202, 260, 316, 351, 358, 362 or 366 in the alpha subunit have been substituted, there is no disclosure of other NDOs or dioxygenases comprising any substitution in the alpha subunit, the critical structural elements an NDO or dioxygenase should have to display the desired activity, or which amino acids in any polypeptide having NDO or dioxygenase activity can be substituted without losing activity. As indicated previously, the state of the art clearly teaches the unpredictability of isolating functional homologs based on structural similarity. See the teachings of Bork (Genome Research, 10:398-400, 2000), Broun et al. (Science 282:1315-1317, 1998), Seffernick et al. (J.

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Bacteriol. 183(8):2405-2410, 2001) and Witkowski et al. (Biochemistry 38:11643-11650, 1999) already discussed. Since the amino acid structure of a polypeptide determines its function, one of skill in the art would require some knowledge or guidance as to how structure correlates with function. Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge about the critical structural elements required to maintain the desired function, and the unpredictability of the prior art in regard to isolation of functional homologs based on structural similarity, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to (1) screen and isolate those polypeptides, as encompassed by the claim, with NDO or dioxygenase activity, (2) determine which amino acid substitutions can be made in such polypeptides and retain the desired function, and (3) determine the function of the fragments as encompassed by the claims. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims rejected under 35 U.S.C. 102(b) as being anticipated by Jiang et al. (J. Bacteriol. 178(11):3133-3139, 1996). Jiang et al. teaches the site-directed mutagenesis of amino acids in the alpha subunit (large subunit of terminal oxygenase, Abstract, line 3) of toluene dioxygenase (TDO) from *Pseudomonas putida* F1. Jiang et al. teaches several mutants of the alpha subunit of TDO (Table 2, page 3136, second column) including some with some residual TDO activity such as Tyr221Ala and Tyr266Ala. Claims 1-8, 11-12, 30-37 are drawn to any NDO or any

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dioxygenase complex comprising any amino acid substitution in the alpha subunit, or fragments thereof. See claim interpretation in claim rejections under 35 USC 112, second paragraph. As such, the teachings of Jiang et al. anticipate the claims as written.

19. Claims rejected under 35 U.S.C. 102(b) as being anticipated by Mondello et al. (Applied and Environmental Microbiology 63(8):3096-3103, August 1997). Mondello et al. teaches the amino acid substitution of several amino acids in the alpha subunit (large subunit of the terminal dioxygenase; BphA; column 1, page 3096, line 7) of biphenyl dioxygenase (Abstract, Table 1, page 3098). Mondello et al. also teaches that many of these mutated alpha subunits can improve polychlorinated biphenyl (PCB) degradation (Table 5, page 3102). Claims 1-8, 11-12, 30-37 are drawn to any NDO or any dioxygenase complex comprising any amino acid substitution in the alpha subunit, or fragments thereof. See claim interpretation in claim rejections under 35 USC 112, second paragraph. As such, the teachings of Mondello et al. anticipate the claims as written.

Double Patenting

20. It is noted that while claim 13 has been objected since it is partially drawn to non-elected inventions, if amended to recite only SEQ ID NO: 14 or 15 (or SEQ ID NO: 2), the claim will be rejected as being a duplicate of claim 10 since SEQ ID NO: 14, 15 and 2 are identical.

Conclusion

21. No claim is in condition for allowance.

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22. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.

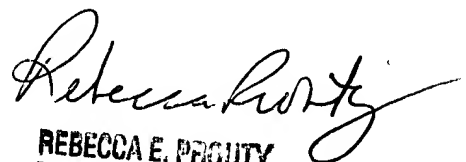
23. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
February 28, 2003


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1600